147. An antibody or antigen-binding fragment thereof having binding specificity for a naturally-occurring human C-C chemokine receptor 3 protein, wherein said naturally-occurring human C-C chemokine receptor 3 protein is encoded by a nucleic acid that hybridizes under moderate stringency conditions to a second nucleic acid consisting of the nucleotide sequence SEQ ID NO:3 or the complement thereof, and the antibody or antigen-binding fragment inhibits binding of a ligand to the receptor and inhibits function associated with binding of the ligand to the receptor.

148. The antibody or antigen-binding fragment of Claim 144 or 146 wherein said C-C chemokine receptor 3 protein is encoded by a nucleic acid that hybridizes under high stringency conditions to a second nucleic acid consisting of the nucleotide sequence SEQ ID NO:3 or the complement thereof.

149. The antibody or antigen-binding fragment of Claim 145 or 147 wherein said C-C chemokine receptor 3 protein is encoded by a nucleic acid that hybridizes under high stringency conditions to a second nucleic acid consisting of the nucleotide sequence SEQ ID NO:3 or the complement thereof.

E11 ant

150. The antibody or antigen-binding fragment of Claim 49 wherein said antibody or fragment is a humanized or chimeric antibody or a humanized or chimeric antigen-binding fragment.---

REMARKS

Claims 75-86 were added in the Preliminary Amendment filed on August 4, 2000. Claims 38, 39, 49-51, 53, 55, 59-62, 65, 67, 69-73, 75 and 77-81 have been amended and Claims 87-150 have been added to the application. Claims 38, 39, 49-51, 53, 55, 57-150 are pending. Claims 59-67 and new Claims 104-118 are directed to a non-elected invention.

Claims 38, 49, 53, 59, 61, 65, 70, 71, 73 and 75 have been amended to recite that the C-C chemokine receptor 3 protein is encoded by a nucleic acid that hybridizes under moderate stringency conditions to a second nucleic acid consisting of a specified nucleotide sequence.

Claims 38, 39, 49-51, 53, 55, 59, 60-62, 65, 67, 69, 70-73, 75 and 81 have been amended to replace "antigen binding" with "antigen-binding".

Claims 38, 70, 71 and 73 have been amended to recite "having binding specificity".

Claims 59 and 61 have been further amended to recite "naturally-occurring mammalian chemokine receptor 3 protein" and to delete "or portion thereof".

Claims 65 has been further amended to recite "naturally-occurring human chemokine receptor 3 protein" and to delete "or portion thereof".

Claim 77 has been amended to delete "and wherein said antibody or fragment can compete with monoclonal antibody 7B11 for binding to a human C-C chemokine receptor 3 protein comprising the amino acid sequence of SEQ ID NO:2".

Claim 78 has been amended to depend from Claim 77 and to delete "said antibody or fragment comprises the light chain CDRs (CDR1, CDR2 and CDR3) and the heavy chain CDRs (CDR1, CDR2 and CDR3) of monoclonal antibody 7B11, and wherein".

Claim 79 has been amended to delete "can compete with monoclonal antibody 7B11 for binding to a human C-C chemokine receptor 3 protein comprising the amino acid sequence of SEQ ID NO:2, and".

Claim 80 has been amended to depend from Claim 79 and to delete "and is a humanized immunoglobulin or antigen-binding fragment comprising the light chain CDRs (CDR1, CDR2 and CDR3) and the heavy chain CDRs (CDR1, CDR2 and CDR3) of monoclonal antibody 7B11 and a human framework region".

Support for the C-C chemokine receptor 3 being encoded by a nucleic acid that hybridizes under moderate or high stringency conditions is found throughout the specification, for example, at page 23, line 10 to page 25, line 21.

Support for the C-C chemokine receptor comprising the amino acid sequences recited in the claims is found throughout the specification, for example, at Figure 1A-1C, Figure 2A-2B, page 23, line 27 *et seq.* and page 45, line 4 *et seq.*

Support for the ligand being MCP-3, RANTES, MCP-2, MCP-4 or eotaxin is found at page 17, line 29 to page 18, line 12 and at page 38, lines 16-22, for example.

Support for the claimed compositions is found at page 70, lines 12-26.

Support for the antigen-binding fragment being a Fab fragment, a Fab' fragment, a $F(ab')_2$ fragment or a Fv fragment is found at page 38, lines 23-27, for example.

Support for the antibody or antigen-binding fragment being a humanized or chimeric antibody or an antigen-binding fragment thereof is found at page 39, line 3 to page 40, line 14.

The amended claims and new claims find support in the specification and claims as originally filed. Therefore, this Amendment adds no new matter.

Additional remarks are set forth below with reference to the numbered paragraphs in the Office Action dated August 4, 1999 (Paper No. 14).

Request for Interview

Applicants request an interview with the Examiner prior to further action on the merits. The Examiner is invited to telephone Helen E. Wendler, Esq. at (781) 861-6240 to arrange a convenient date and time.

Paragraph 6. Rejection of Claims 49 and 53 Under 35 U.S.C. § 112, First Paragraph

Claims 49 and 53 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one of skill in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner states that the specification teaches antibodies that bind human CKR3 (Office Action dated December 16, 1998 at page 4, lines 18-20), but that the specification does not disclose other mammalian CKR3 proteins by amino acid sequence or other relevant identifying characteristics (e.g., structure, physical and/or chemical properties). The Examiner further states that the description of mammalian CKR3 proteins is limited to their function and to methods for isolating the proteins from their natural sources, which is not sufficient to fulfill the written description requirement.

Claims 49 and 53, as well as Claims 38, 59, 61, 65, 70, 71, 73 and 75, have been amended as described above to more clearly define the invention. The amended claims recite structural and functional features of mammalian CCR3 receptors and are fully supported by the specification as filed. Accordingly, the disclosure of the subject patent application conveys with reasonable clarity to those skilled in the art, that Applicants were in possession of the claimed invention at the time the application was filed. No more is necessary to fulfill the written description requirement of 35 U.S.C. § 112, first paragraph. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555; 19 USPQ2d 1111 (Fed. Cir. 1991).

Reconsideration and withdrawal of the rejection are respectfully requested.

Paragraph 7. Rejection of Claims 38-39, 49-51, 53, 55, 57-58 and 68-74 Under 35 U.S.C. § 112, First Paragraph

Claims 38-39, 49-51, 53, 55, 57-58 and 68-74 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not disclosed in the specification in such a manner as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In maintaining the rejection, the Examiner states that the claims refer to "C-C chemokine receptor 3 protein" and that this phrase, does not convey distinguishing information or inherently correspond to any particular chemokine receptor protein. The Examiner further states that the person of ordinary skill in the art would be unable to make and use the claimed antibody molecules without undue experimentation because one could not distinguish the chemokine receptor proteins envisaged by the specification from those which are unrelated.

The amended claims encompass antibodies and antigen-binding fragments which bind to a C-C chemokine receptor 3 protein that is encoded by a nucleic acid that hybridizes under moderate stringency conditions to a second nucleic acid consisting of the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3 or SEQ ID NO:5. At the time the application was filed, the person of ordinary skill in the art would have been able to make and/or use antibodies or antigen-binding fragments embraced by the claims by following the teaching of the specification or using other methods that were known in the art.

Evidence that the specification contains an enabling disclosure is provided by Sabroe, I. *et al.* (*J. Immunol., 161*:6139-6147 (1998)) (cited as reference AT3 in the Information Disclosure Statement filed concurrently). Sabroe *et al.* describe a study in which a nucleic acid encoding guinea pig CCR3 was isolated and cloned based upon hybridization with cDNA probes encoding human and mouse CCR3 (see, Materials and Methods, under the subheading "Isolation of guinea pig CCR3 genomic bacteriophage clones"). Sabroe *et al.* also describe the production of monoclonal antibodies by immunizing C57BL6 mice with transfected L1.2 cells that expressed the guinea pig CCR3, followed by fusing splenic lymphocytes isolated from the immunized mice with SP2/0 myeloma cells to generate antibody producing hybridomas (page 6141, left column under the heading "Generation of anti-guinea pig CCR3 receptor antibodies and flow cytometry"). Sabroe *et al.* further describe the isolation of mAb 2A8 which inhibited the binding of ligand to the receptor, ligand-induced chemotaxis and ligand-induced calcium flux (see, for example, the Abstract). It is noted that the methods that were successfully used by Sabroe *et al.*

are well known in the art and/or are similar to the methods that Applicants describe in their specification. (See, for example, page 78, lines 11-23 regarding hybridization; and page 115, lines 1-32 *et seq.* regarding hybridoma production).

In view of the forgoing it is clear that Applicants' specification contains a disclosure that is sufficient to enable one skilled in the art to make and/or use the claimed invention using no more than routine experimentation. Reconsideration and withdrawal of the rejection are requested.

Paragraph 8. Rejection of Claims 38-39, 49-50 and 70-71 Under 35 U.S.C. § 103

Claims 38-39, 49-50 and 70-71 are rejected under 35 U.S.C. § 103 as being obvious over Yamagami *et al.* (*Biochem. Biophy Res. Comm. 202*(2):1156-1162 (1994)) in view of Lerner (*Nature 299*:592-596 (1982)) and Harlow *et al.* (Antibodies: A Laboratory Manual, Chapter 5, page 76, Cold Spring Harbor Laboratory (1988)). The Examiner states that Yamagami *et al.* disclose the cDNA cloning of a human monocyte chemoattractant protein 1 receptor which has a stretch of 10 amino acids identical with a portion of the amino acid sequence depicted in SEQ ID NO: 2 of the present application and that the stretch of identical amino acids are not part of the transmembrane domain. The Examiner further states that Lerner teaches the production of antibodies from known polypeptides, wherein the antibody can have predetermined specificity and that antibodies made against a predetermined peptide are useful in studying the protein conformation of the intact protein from which the immunizing peptide was cleaved. The Examiner also states that Harlow *et al.* teach that peptides of six residues in length will consistently elicit antibodies that bind to the original protein. The Examiner concludes that it would have been *prima facie* obvious to one having ordinary skill in the art to use the amino acid sequence taught by Yamagami *et al.* to produce monoclonal and polyclonal antibodies with a predetermined specificity as taught by Lerner with the expectation that the antibodies made against proteins with sequence identity to SEQ ID NO: 2 would be useful in understanding the conformational changes the receptor undergoes during activation by a natural ligand.

In maintaining the rejection, the Examiner states that the sequence of 10 amino acids that she has identified as being identical with a portion of SEQ ID NO:2 is exemplary since there are many other regions of amino acid sequence identity. The Examiner further states that an antibody which binds the MCP-1RB receptor (CCR2B) would certainly bind the CCR3

polypeptide and inhibit function associated with binding of ligand to the receptor, and that it would be difficult to make an antibody that did not bind to both receptors.

The Examiner has provided an alignment of the amino acid sequence of SEQ ID NO:2 and the amino acid sequence of MCP-1RB (CCR2B) reported by Yamagami *et al.* and relies on the alignment for demonstrating that the proteins contain regions of amino acid identity. However, inspection of the alignment in view of the teachings of Yamagami *et al.* reveals that the regions of amino acid identity are clustered in the transmembrane and intracellular portions of the two receptors. An annotated copy of the alignment, on which the predicted extracellular regions (EC1-EC4), predicted transmembrane regions (TM1-TM7) and predicted intracellular regions (IC1-IC4) have been identified in accordance with the teachings of Yamagami *et al.* (see, Yamagami *et al.* at Figure 1), is provided herewith (Exhibit; predicted extracellular, transmembrane and intracellular regions are labeled and predicted transmembrane and cytoplasmic domains are highlighted). The alignment does reveal areas of limited amino acid sequence identity which are within the extracellular domains of SEQ ID NO:2 and MCP-1RB, with the longest stretch of amino acid sequence identity that is not part of the transmembrane domains or intracellular domains being four amino acids (see, extracellular domain II). However, according to Harlow *et al.*, "[t]he smallest synthetic peptides that will consistently elicit antibodies that bind the original protein are 6 residues in length" (Harlow *et al.* at page 76, first sentence under the heading "Size of the Peptide"). In addition, Lerner teaches, "[t]he minimum size of the peptide chosen [to elicit antibodies] is important and should be larger than six amino acids" (Lerner at page 596, first column, line 13). Thus, SEQ ID NO:2 and MCP-1RB have no regions of amino acid sequence identity which are found in exposed domains that meet the criteria of Lerner and Harlow *et al.* for use in producing antibodies which bind native protein. Thus, the person of ordinary skill in the art would not have expected that an antibody raised against a peptide derived from MCP-1RB would bind to SEQ ID NO:2 and could be used to study ligand-induced conformational changes of a protein SEQ ID NO:2 as suggested by the Examiner. Moreover, it is clear that the rejection relies on the skilled man knowing which regions of SEQ ID NO:2 and MCP-1RB are identical in order to prepare such antibodies, and in assuming that the skilled man knows the sequence of SEQ ID NO:2 (which is not found in the prior art) improperly relies on hindsight.

Moreover, with regard to the regions of amino acid identity between SEQ ID NO:2 and MCP-1RB (CCR2b) that are within the predicted transmembrane or intracellular domains, the

person of ordinary skill in the art at the time the invention was made would have known that these regions of MCP-1RB are not exposed on the surface of cells that express MCP-1RB (see Yamagami *et al.* at Figure 1 and page 1160, lines 2-9). Accordingly, the skilled person would not have been motivated to produce antibodies which bind these regions of MCP-1RB with a reasonable expectation that such antibodies could be used for the study of ligand-induced conformational changes or for inhibiting binding of ligand to another receptor, as suggested by the Examiner, because the epitopes bound by the antibodies are within the plasma membrane or in the cytoplasm and thus not accessible to antibodies.

Furthermore, even if it were possible to prepare antibodies which fortuitously bound CCR3 by immunizing animals with peptides derived from MCP-1RB (CCR2), the claimed invention would be considered nonobvious because the combined teachings of the cited references do not teach the desirability or direct the skilled person to prepare antibodies using peptides derived from regions of MCP-1RB (CCR2) which have sequence identity to other chemokine receptors. In fact, Yamagami *et al.*, teach that the amino acid sequence of MCP-1RB is "highly homologous" to known chemokine receptors in the N-terminal region, in the predicted second cytoplasmic region (which includes the 10 amino acid peptide identified by the Examiner) and in the predicted transmembrane regions. Thus, the person of ordinary skill would have concluded that any antibody raised against a peptide derived from regions of MCP-1RB which shares amino acid sequence identity with other known chemokine receptors would bind to multiple polypeptides. Such an antibody would be undesirable because the primary motivation for producing antibodies is to distinguish a selected polypeptide from other proteins based upon antibody binding and to allow for specific targeting of the polypeptide for therapeutic, diagnostic or research applications. Thus, Yamagami *et al.* teach away from selecting a peptide that has amino acid sequences that are identical to those of other proteins (e.g., peptides derived from the N-terminal region, the second cytoplasmic region and in the transmembrane regions of MCP-1B) for use in preparing antibodies, because the antibodies would be expected to bind multiple proteins.

As noted above, the Examiner also states, "[a]n antibody to the MCP-1RB receptor of the prior art would certainly bind to the instant chemokine receptor polypeptide and inhibit function associated with binding of the ligand to the receptor, in fact it would be difficult to make an antibody that did not bind to both the receptors" (Office Action at Page 5, line 19 to Page 6, line 2). The Examiner's statement appears to contradict contemporary understanding of

antibody/receptor interactions. In particular, it is scientifically improper to conclude that an antibody which binds MCP-1RB "would certainly bind...and inhibit function" of CCR3, because MCP-1RB and CCR3 are distinct receptors with unique amino acid sequences (discussed in detail above). Furthermore, it is well established in the art that antibodies which bind a receptor do not necessarily inhibit ligand binding or receptor functions associated with ligand binding.

Reconsideration and withdrawal of the rejection are respectfully requested.

Information Disclosure Statement

An Information Disclosure Statement is being filed concurrently. Acknowledgment of consideration of the information provided therein is requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call Helen E. Wendler, Esq. at (781) 861-6240.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Robert H. Underwood

Robert H. Underwood
Registration No. 45,170
Telephone (781) 861-6240
Facsimile (781) 861-9540

Lexington, Massachusetts 02421-4799
Dated: September 20, 2000